

Isoniazid treatment in children and comparison of tuberculin skin test values before and after treatment

Isoniazid prophylaxis in children

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Abstract

Aim: In this study, it was aimed to evaluate the six-month isoniazid treatment and to compare Tuberculin Skin Test values before and after treatment in children with tuberculosis contact and latent tuberculosis infection.

Material and Method: The study included children older than 1 month and younger than 18 years of age who were started on isoniazid prophylaxis. In the treatment of latent TB infection, isoniazid was planned for six months. After the treatment, the tuberculin skin test was reapplied to all patients.

Results: A total of 106 pediatric patients (25.6%) with tuberculosis contact and 81 (76.4%) with latent tuberculosis infection were included in this study. The mean pre-treatment tuberculin skin test value of the patients was 16.57 ± 4.124 mm and 15.07 ± 4.017 mm after treatment. The average tuberculin skin test values before and after treatment were found to have a 1.5 mm difference and the tuberculin skin test values after treatment were found to be lower ($t = 3.5$, $p < 0.01$). However, the number of patients who had increased, unchanged or decreased less than five millimeters tuberculin skin test values after treatment was 80 (75.5%), and the ratio of those with a reduction of five mm and more was only 24.5%.

Discussion: In previous studies, it has been concluded that isoniazid prophylaxis is effective in the prevention of tuberculosis and tuberculin skin test cannot be used to evaluate the efficacy of the treatment of latent tuberculosis infection. Recently, studies on the effectiveness of the treatment of latent tuberculosis infection and new diagnostic tests have become prominent, and we think that our study may draw attention to this issue in our country. It was concluded that tuberculin skin test is not adequate in evaluating the efficacy of treatment, the compliance with the six-month isoniazid treatment in children is good, and the treatment is well tolerated and effective.

Keywords

Children; Isoniazid; Tuberculosis infection; Tuberculin skin test

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Introduction

Despite the advances in the diagnosis and treatment of tuberculosis (TB), it is an important public health problem in the world and in our country. Although one-third of the world's population is reported to be infected with TB, the incidence of latent tuberculosis infection (LTBI) is not fully known. Today, there is still no reliable biomarker showing the treatment efficacy of LTBI. Childhood TB usually develops after contact with adult or adolescent patients with pulmonary TB. Contact is usually within the home, but may also be in school, nursery, nursing home or other enclosed spaces [1,2]. Latent tuberculosis infection identifies the condition where after the inhalation of *M. tuberculosis* into the lungs, it is limited by the host immune response and there are no clinical and radiological findings of TB disease. The diagnosis of latent tuberculosis infection is established by detecting enhanced immunity against *M. tuberculosis* using TST or interferon-gamma release tests (IGRT) [3]. The risk of disease progression is 10% in adults, and the risk of developing active disease is higher in pediatric patients. Due to the high risk of progression to active LTBI in infants and children under five years of age, the inverse proportion of the strength of infection with age, long-term risk developing clinical infection in children with latent infections later, and the increased infectiousness of children reaching adulthood, LTBI treatment is the most important step in TB prevention [1]. INH has been the first choice in the treatment of latent tuberculosis infection for years. The success rate of the treatment with isoniazid for six to nine months is 60-90%. It has been shown that the effect of INH treatment lasts up to 19 years if there is no re-infection with tuberculosis [4]. Due to low compliance with isoniazid treatment for six-nine months, short-term treatment regimens have emerged. It has been reported that compliance with treatment was higher in patients who received INH and rifampicin for three months compared to patients receiving isoniazid alone for six months [1].

The tuberculin skin test is associated with delayed-type hypersensitivity to tuberculin and is an indicator of cellular immunity in humans. Although new biomarkers are being researched, there is currently still no test revealing the success of treatment after the treatment of latent tuberculosis infection. In this study, we aimed to evaluate whether there is variability in TST values after latent tuberculosis infection in pediatric patients, especially whether there is a decrease or not, and the relationship between the variability and clinical and demographic data. Meanwhile, another aim of this study was to evaluate the compliance of children to 6-month INH treatment and the side effects, which may develop as a result of treatment.

Material and Methods

The study included children who had undergone INH treatment due to LTBE and TB contact who were older than one month and younger than 18 years of age. Ethics committee approval was obtained for this study. Written and oral consent were obtained from the parents of the patients. This study was conducted retrospectively. The causes of TST in patients included in the study were recorded. Latent tuberculosis infection was defined as the absence of clinical signs and symptoms consistent with TB, normal chest X-ray, and TST positivity. Tuberculin skin test

positivity was considered for those without a Bacille Calmette Guérin (BCG) scar as 10 mm and above values, and as 15 mm and above for those with a BCG scar, regardless of the number of scars (T.C. Sağlık Bakanlığı Tanı ve Tedavi rehberi/ T.R. Ministry of Health Diagnosis and Treatment guide. 2019)

It was understood that for the Tuberculin Skin Test, 0.1 milliliter 5TU PPD solution was applied to the anterior surface of the left forearm using a 1 ml dizyem-adjustable injector with a 27-gauge needle. The measurement was done with a transparent flexible ruler by using the pen tip method. Tuberculosis contact was defined as contact with an adolescent or adult with pulmonary TB. People living in the same house were accepted as close contact. Close contacts of all the patients included in the study were examined for tuberculosis by using TST at VSD and lung x-ray with microfilm method. It was planned that the course of isoniazid treatment would last six months. The patients were reevaluated in the first week, and at one, two, three and six months. The patients were questioned about compliance with the treatment and drug side effects by interviewing the patient and their families when they came to the control. The patient's body weight was measured and a dose adjustment was made if necessary. TST was reapplied to all patients after treatment. The tuberculin skin test was performed by trained health professionals and evaluated by the pencil tip method. Cases with increased TST values after treatment were evaluated in terms of the possibility of developing active disease.

Statistical Analysis

Descriptive statistics of continuous data were given using mean \pm standard deviation, median (minimum-maximum) values, and descriptive statistics for categorical data were given using percentages. Pre- and post-treatment TST values were compared using paired T-Test and universal mean significance test. SPSS for Windows (ver. 11.0) package program was used for statistical analysis. A p-value <0.05 was considered statistically significant.

Results

Demographic characteristics

A total of 106 patients, of which 25 (23.6%) had TB contact, were enrolled in the study. Among the patients included in the study, The TST value was positive in 101 patients, and negative in 5 patients with TB contact history. Fifty-four (50.9%) patients were female and 52 (49.1%) were male. The ages of the patients were between 2 and 14 years, and the mean age was 8.18 ± 2.38 years. The reasons for performing TST for the patients included in the study are shown in Table 1.

INH treatment compliance and side effects

Ninety-eight (92.5%) patients completed the six-month INH treatment without interruption. It was learned that eight patients had disrupted treatment due to gastrointestinal symptoms such as abdominal pain, nausea and vomiting. Four of these patients (3.8%) were not treated for five days, one (0.9%) for seven days, two (1.9%) for 10 days and one (0.9%) for 15 days. None of these patients had increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, and these patients were advised to take their medication with meals. The patient's complaints did not recur after this change. Thus, all patients completed six months of treatment.

Table 1. Distribution of Patients According to Reasons for Tuberculin Skin Testing

Reason for Tuberculin skin test	Number (n)	Percentage (%)
School screening	66	62,29
Complaint	9	8,49
Family screening	29	27,35
Before delayed vaccination	2	1,88

Table 2. Distribution of patients according to changes in the Tuberculin skin test values before and after treatment

Change in tuberculin skin test value	Number (n)	(%)
+ 15 mm	1	0,9
+ 8 mm	1	0,9
+ 7 mm	2	1,9
+ 5 mm	5	4,7
+ 4 mm	3	2,8
+ 3 mm	4	3,8
+ 2 mm	7	6,6
+ 1 mm	8	7,5
0 mm	9	8,5
- 1 mm	10	9,4
- mm	14	13,2
- 3 mm	10	9,4
- 4 mm	6	5,7
- 5 mm	12	11,3
- 6 mm	4	3,8
- 7 mm	2	1,9
- 8 mm	2	1,9
- 9 mm	2	1,9
- 10 mm	2	1,9
- 11 mm	1	0,9
- 12 mm	1	0,9
Total	106	100

Since there was no interruption of more than 15 days, the treatment was not prolonged for any patient. Eleven patients (10.3%) developed ALT elevation not exceeding the norm by 1.5 times. In these patients, it was observed that enzyme levels decreased to normal without the need to interrupt treatment. None of the patients had severe hepatic dysfunction.

Tuberculin skin test values

Tuberculin skin test showed an increase of less than five mm in 22 (20.75%) cases, and five mm or more in 9 (8.4%) cases after treatment. In 49 (46.22%) cases, there was less than 5 mm, and in 26 (24.5%) cases there was a 5 mm or more decrease in TST values. The mean TST value in the patients before treatment was 16.57 ± 4.124 mm and 15.07 ± 4.017 mm after the treatment. The mean difference between the pre- and post-treatment TST values was 1.5 mm, and the post-treatment TST values were found to be lower ($t=3.5$ $p<0.01$). Table 2 shows the distribution of patients according to the change in TST before and after treatment. None of the patients with increased TST after treatment had any clinical and radiological findings of active disease.

There was no statistically significant difference in the mean age, gender, BCG scar count, contact presence, socioeconomic status in patients with a decrease of 5 mm in their TST values after treatment compared to the pre-treatment levels ($p>0.05$).

Discussion

There are two tests in determining latent tuberculosis infection: TST and IGRTs. The tuberculin skin test is performed using the 'Mantoux, technique, which includes the intradermal injection of the five tuberculin units (TU) of the PPD-S purified protein derivative (PPD) or the two TUs of PPD RT23. In a person with cellular immunity to these tuberculin antigens, a delayed-type hypersensitivity reaction develops after 48-72 hours. This reaction causes an induration localized at the injection site [1,5]. It is well known that non-tuberculous mycobacteria can induce tuberculin sensitivity. Bacille Calmette-Guérin vaccine can also cause false- positive TST by cross-reaction with mycobacterial antigens. Interferon Gamma Release tests are the laboratory alternative to TST in the diagnosis of LTBI. Interferon Gamma Release assays are "ex vivo" tests that measure T cell response after stimulation with specific antigens relative to *M. tuberculosis*. These tests are a direct marker of *M. tuberculosis* exposure and show a cellular immune response to *M. tuberculosis* [5]. In our study, LTBI was diagnosed with TCT. The change in TCT after INH prophylaxis in people with latent tuberculosis infection started to be studied after the 1950s, when this drug was put into use. In the early studies, it has been reported that a significant number of patients may become TCT negative after treatment [6-8]. However, in two studies conducted in the 1980s, these data could not be verified [8,9]. In a study that included 370 children with latent tuberculosis infection and followed up for three to nine years, the effect of INH treatment on the TST in the long term and whether the disease became active after INH prophylaxis was evaluated. In this study, 23.4% of patients had increased TST by 5 mm or more, 21.6% had a change of less than 5 mm, and 55% had a decrease of 5 mm or more. It was determined that TST was not negative in any of the patients. The researchers concluded that INH treatment prevents LTBI from progressing to active disease, but that TST positivity still persists, which is in fact beneficial for the patient, and that ongoing cellular mediated immunity may be protective against future exogenous re-infections [9]. In another study, it was stated that in patients who received INH chemoprophylaxis, a single negative TST after treatment or negative results obtained several times after a short period of treatment should not be considered as a negative TST. The authors emphasized that the loss of tuberculin reactivity can only be confirmed by in vitro tests, by the evaluation of lymphocyte proliferation and lymphokine release in response to PPD [10]. In our study, in children who had undergone six months of INH prophylaxis, repeated TST at the end of treatment showed an increase of less than five mm in 20.75% of patients after treatment and by 5 mm or more in 8.4% of patients after treatment. There was a 1.5 mm decrease in TST values before and after treatment, and this difference was found to be statistically significant. However, the number of patients who had increased, unchanged or decreased less than five millimeters tuberculin skin test values after treatment

was 80 (75.5%), and the ratio of those with a reduction of five mm and more was only 24.5%. In our study, there were no patients who became TST negative after treatment. The signs and symptoms suggestive of active disease did not develop in patients with elevated TST after treatment. Among the patients with an increase compared to pre-treatment, 41.9% are TB contact patients, and it is known that the TST values in these patients may be increased after contact. One of the reasons for this increase in patients with increased TST after treatment may be the booster phenomenon. The Booster phenomenon is defined as a decrease in tuberculin reactivity over time due to a decrease in cellular immunity in patients sensitized with BCG vaccine or *M. tuberculosis*, and a significant increase in TST values if TST is repeated in a week to one year [11]. According to our study, it was thought that evaluating the effectiveness of treatment according to the reapplication and negativity of TST after LTBI treatment was not appropriate. The hypothesis that T cell IFN- γ responses to *Mycobacterium tuberculosis* specific antigens will be reduced by the reduction of disease activity with TB treatment suggested that IGRTs can be used to monitor response to treatment. Although there were few studies supporting this view, in two large trials with 275 patients and 149 patients with active TB, serial IGRT measurements and sputum smear and culture results have been compared and no relationship has been found, most patients remained IGRT positive [12,13]. Both TST and IGRTs were not accepted as tests to verify *M. tuberculosis* was eradicated when LTBI treatment was completed. Very recently, in order to detect biomarkers that can potentially correlate with treatment success, changes in mycobacteria-specific antigens-induced cytokines in patients receiving latent or active TB treatment were investigated. Thirty-three adult patients with active TB and thirty-six with active TB were followed longitudinally throughout the treatment. Whole blood stimulation test was performed at zero, one, three, six and ninth months using mycobacteria-specific antigens (CFP-10, ESAT-6, PPD), and cytokine responses in supernatants (IFN-10, IL-1ra, IL-2, IL-10, IL-13, IP-10, MIP-1 β , and TNF-IP) were measured. In cases of active TB, the median IL-1ra, IP-10, and TNF-2 responses, as well as in cases of latent TB, the median IL-1ra, IL-2 and IP-10 responses were significantly reduced during the course of the treatment. The researchers concluded that mycobacteria-specific cytokine responses changed significantly over the course of treatment and that their kinetics differed in active TB and latent TB, particularly mycobacterial-specific IL-1ra responses were correlated with treatment success in both active and latent TB [2].

An important role of tuberculosis control programs is the identification of individuals with LTBI at risk of developing active TB. Treatment of patients with latent tuberculosis infection provides benefits for both one's own health and public health. Immediately after the discovery of isoniazid in 1952, it has been used both as a component of active TB infection treatment and for the prevention of the development of active disease in patients who encounter the TB bacillus [9]. If INH treatment is administered properly and without disruption, its efficacy is greater than 90%. However, 64-67% or less of the patients have been reported to have completed the treatment due to the length of treatment. People with latent tuberculosis

infection may not be willing to continue treatment because they are not clinically ill [14]. In a study of 105 children and adults diagnosed with latent tuberculosis infection, 28.5% of patients were found to interrupt treatment at least once [15]. Nowadays, although the most commonly used LTBI treatment is six to nine months of INH treatment, rifampicin for four months, rifampicin together with INH for three to four months, and treatment regimens with rifapentine once a week for 3 months are also proposed to improve compliance [16-18]. In a study comparing treatment compliance between a 4-month rifampicin treatment and 9-month INH treatment for latent tuberculosis infection, the compliance with treatment was 91% in the rifampicin group and 76% in the INH group [14]. In a retrospective large-scale study, 2149 patients were evaluated and similarly, treatment compliance to the rifampicin treatment was found to be 72%, while it was 53% in the INH group [19]. In our study, patients with tuberculosis contact and LTBI diagnosis were given INH for six months. Full compliance with the treatment was determined in our patients. In our study, the reasons for the higher compliance with the treatment compared to the data in the literature were thought to be the inclusion of only pediatric patients in the study, sufficient information given about the importance of adherence to the treatment to the parents of the children in the study, and the patients being given the medication by their parents. The side effects of isoniazid, hepatotoxicity and peripheral neuritis can prevent the completion of treatment. The rate of transient liver enzymes level increase due to isoniazid use is 10-20%, but the rate of severe hepatotoxicity is reported as 2% [20-22]. In a large 7-year study including 11,141 patients, only 11 patients developed hepatotoxicity, and no fatalities were observed in any of these patients. The authors emphasized the importance of using current guidelines for patient selection for treatment, the importance of patient education and evaluation of patients monthly [23]. In our study, 10.3% of patients had transient ALT elevation not exceeding 1.5 times normal levels. None of our patients had severe hepatotoxicity. In our study, because of the complaints of gastrointestinal intolerance in 7.5% of the patients, the treatment was temporarily stopped, and after which the treatment was completed. In the first weeks of isoniazid treatment, loss of appetite, nausea and vomiting may be seen. Although the intake of the drug with food delays or decreases its absorbance, this effect has little clinical importance. The guidelines for TB treatment published by the American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) in 2016 recommends dividing the treatment dosage or taking the medication with meals, in cases where epigastric discomfort and nausea develop with first-line treatment [24]. In our study, patients who developed gastrointestinal complaints were advised to take their medication with food. Complaints did not recur when this advice was followed.

As a result, in previous studies, it has been concluded that isoniazid prophylaxis is effective for the prevention of tuberculosis, and tuberculin skin test cannot be used to evaluate the efficacy of the treatment of latent tuberculosis infection. Nowadays, studies on the effectiveness of the treatment of latent tuberculosis infection and new diagnostic tests have

become prominent, and we think that our study may draw attention to this issue in our country.

The co-evaluation of two separate groups of tuberculosis contact and latent tuberculosis infection, and the inability to perform the tuberculin skin test by the same person, were the limiting aspects of our study.

Conclusion

After six months of INH treatment/prophylaxis in children with latent tuberculosis infection or TB contact, there was a statistically significant decrease of 1.5 mm in TST. However, only one fourth had a decrease of 5 mm or more, and no patient had a negative TST, therefore, it was concluded that TST was not sufficient in the evaluation of treatment efficacy after treatment of LTBI with INH. None of the patients developed active TB disease, including those with increased TST after the treatment. It has been shown that good compliance to six months of INH treatment in children can be reached by sufficiently informing the parents about the importance of compliance with treatment and the parents administering the medication themselves. Thus, when gastrointestinal intolerance complaints develop, treatment can be completed by taking the drug with food, while a mild increase in transaminase level during treatment does not require discontinuation of the treatment so that no serious hepatotoxicity developed and for the treatment to be effective. Large prospective studies are needed to evaluate biomarkers of treatment efficacy, using tests based on measuring changes in cytokines induced by mycobacteria-specific antigens, which have recently been reported as promising.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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